



Application No. 10/801,648

Docket No.: V9661.0074

AMENDMENTS TO THE DRAWINGS

Please cancel the amendment to Figure 1A presented in the "Amendment in Response to Non-Final Office Action" filed June 30, 2006, and reinstate Figure 1A as originally filed.

REMARKS

In the Office Action dated September 20, 2006, the specification remains objected to for certain informalities and under 35 U.S.C. § 132(a), respectively.

Claims 13-16 and 23-26 are objected to for certain informalities.

Claims 13-16, 23-26 and 29-33 and 35-47 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter.

Claims 13-16, 23-26, 29-33 and 35-40 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement and comprising new matter.

Claims 13-16, 23, 25, 26 and 29-47 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claims 13-16, 23-26 and 29-47 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Non-elected claims 1-9, 17-22, 27 and 28 are herein cancelled.

Further, claims 16, 33, 34 and 40 are herein cancelled.

Claims 13, 23, 26, 29, 35, 37, 41, 43 and 47 are herein amended.

No new matter has been introduced by the amendments.

Claims 13-15, 23-26, 29-32, 35-39 and 41-47 are currently pending in the case.

Reconsideration of the present application in view of the foregoing amendments and the remarks below is respectfully requested.

Objections to the Specification

(1) The disclosure remains objected to because the specification allegedly contains a table of contents.

Applicants respectfully submit that the specification **was** amended by removing the page entitled "TABLE OF CONTENTS" in the previous "Amendment in Response to Non-Final Office Action" ("Amendment") filed June 30, 2006 (please see the first paragraph at page 3 of the "Amendment").

Accordingly, Applicants respectfully request that the objection to the specification under this section be withdrawn.

(2) The amendment to SEQ ID NO:1 in the "Amendment" filed June 30, 2006 is objected to under 35 U.S.C. § 132(a) as allegedly introducing new matter into the disclosure.

Applicants respectfully traverse the objection.

In the present specification, the construction of AAV vectors containing the nucleotide sequence encoding human bone morphogenetic protein-2 (BMP2) and the expression of BMP-2 in C2C12 cells and SD rats are disclosed throughout the present specification. In particular, Figure 2 and Section 6 "Examples" at page 35 of the specification explain in detail how the AAV vector containing the nucleotide sequence encoding BMP2 is prepared. Specifically, the vector plasmid pAM/CAG-BMP2 is constructed by cloning **human BMP2 cDNA (i.e., the coding sequence of human BMP2)** into the EcoRI and XhoI sites located between two ITRs (please see lines 24-25 at page 35 of the specification and Figure 2).

Meanwhile, at page 6, lines 11-20, the specification states that "[i]n a specific embodiment, said vector comprises an expression cassette which comprises an adeno-associated viral vector (AVV) containing chicken beta-actin promoter with cytomegalovirus (CMV) enhancer (CAG promoter) which is operatively linked to **the**

nucleotide sequence encoding the bone morphogenetic protein having an amino acid sequence of SEQ ID NO:2 or a biologically functional fragment, analog, or variant thereof" (emphasis added). Further, at lines 19-20 on the same page, the specification states, "[i]n one embodiment, ***said nucleotide sequence has a nucleotide sequence of SEQ ID NO:1***" (emphasis added).

These descriptions above clearly indicate that SEQ ID NO:1 is intended to be the ***cDNA*** sequence of human BMP2, ***excluding the non-translated regions of the BMP2 gene***, and encodes the amino acid sequence of SEQ ID NO:2.

It would have been obvious to one skilled in the art to recognize that the sequence of SEQ ID NO:1 as originally filed contains an error by including the non-translated regions, as the number of the nucleotides in SEQ ID NO:1 is 1547, while the number of the amino acids in SEQ ID NO:2 is 396, which should have been encoded by $396 \times 3 = 1188$ (nucleotides), excluding the stop codon.

Furthermore, it would have been without any difficulty for one skilled in the art to figure out which part of SEQ ID NO:1 is the coding sequence for SEQ ID NO:2, because not only the present specification itself discloses the amino acid sequence of human BMP2 (*i.e.*, SEQ ID NO:2) but also the cDNA sequence of human BMP2 was well known in the art at the time when the present application was filed. And recognizing the error, one skilled in the art who compared SEQ ID NOS:1 and 2 in view of the written descriptions regarding the same would have understood that the present inventors had possession of the claimed invention with SEQ ID NO:1 as amended, at the time the application was filed.

Thus, Applicants believe the amendment to the originally filed SEQ ID NO:1 by deleting the non-translated regions is supported by the specification as originally filed and, therefore, does not introduce new matter.

Nevertheless, Applicants herein cancels the amendment to SEQ ID NO:1 and reinstate the original SEQ ID NO:1, as filed, solely to accelerate the prosecution of the case.

Accordingly, the objection to the specification under 35 U.S.C. § 132(a) as allegedly introducing new matter into the disclosure, should be withdrawn.

Claim Objections

Claims 13-16 and 23-26 are objected to because of certain informalities.

Specifically, the Office Action states that claims 13 and 23 each recite “in a body area of an immunocompetent subject where bone regeneration is required.”

Claim 16 is herein cancelled. Accordingly, the objection to claim 16 is now moot.

Claims 13 and 23 are herein amended to recite “where bone regeneration is required to ameliorate said diseases or disorder”, as suggested by the Examiner.

Accordingly, Applicants respectfully request the objections to claims 13-15 and 23-26 be withdrawn.

Claim Rejections under 35 U.S.C. § 112

(1) Claims 13-16, 23-26 and 29-33 and 35-47 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter.

Specifically, the Office Action states that claims 13, 23, 29, 35 and 41 each recite local administration and that “it is unclear how close an administration must be to be considered local.”

Claims 16, 33 and 40 are herein cancelled. Accordingly, the rejections to these claims are now moot.

Claims 13, 23, 29, 35 and 41 are herein amended to recite “administering directly to a skeletal muscle of said body area”.

Further, the Office Action states that claims 13, 23, 29, 35 and 41 each recite “where bone regeneration is required” and the metes and bounds of the term “required” are unclear without a reason for the requirement.

Applicants respectfully disagree with the statement.

While claims 13 and 23 each indeed recite “where bone regeneration is required”, none of claims 29, 35 and 41 recites said phrase, unlike the assertion by the Examiner.

Claims 13 and 23 are herein amended to recite “where bone regeneration is required to ameliorate said disease or disorder,”

Accordingly, Applicants respectfully request that the rejections of claims 13-15, 23-26, 29-32, 35-39 and 41-47 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, be withdrawn.

(2) Claims 13-16, 23-26, 29-33 and 35-40 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement and comprising new matter.

Claims 16, 33 and 40 are herein cancelled and, therefore, the rejections of these claims are now moot.

Specifically, the Office Action states that “Applicant’s amendments of 6/30/06 amend SEQ ID NO:1 to truncate the non-coding sequences in the sequence” and that Applicant has provided no support for possession of such, and any arguments are directed to obviousness.”

Applicants respectfully traverse the rejection for the reasons presented in the section under “Objections to the Specification” (2).

However, Applicants has cancelled the amendment to SEQ ID NO:1 and reinstated the original sequence of SEQ ID NO:1 as filed. Furthermore, claims 13, 23, 37 and 43 each are herein amended to delete the reference to SEQ ID NO:1. Again, these amendments are solely for the purposes of accelerating the prosecution of the case.

Accordingly, Applicants respectfully request that the rejections of claims 13-15, 23-26, 29-32 and 35-39 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement and comprising new matter, be withdrawn.

(3) Claims 13-16, 23, 25, 26 and 29-47 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Specifically, the Office Action states that Applicant has provided no explicit or support for such limitation as “administration of the vector locally to a body area”, while the only specific discussion is that of direct administration to muscle.

Claims 16, 33, 34 and 40 are herein cancelled. Accordingly, the rejection of these claims are now moot.

As discussed in the previous section, claims 13, 23, 29, 35 and 41 are herein amended to recite “administering directly to a skeletal muscle of said body area”.

Accordingly, the rejections of claims 13-15, 23, 25, 26, 29-32, 35-39 and 41-47 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, should be withdrawn.

(4) Claims 13-16, 23-26, and 29-47 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

Claims 16, 33, 34 and 40 are herein cancelled. Accordingly, the rejection of these claims are now moot.

Claims 13, 23 and 29 are herein amended to recite “administering directly to a skeletal muscle of said body area” and further to recite “wherein said disease or disorder is selected from the group consisting of bone fracture non-union, segmental bone defects, spinal fusion, periodontal disease, degenerative disc disease, and growth plate injury” in claims 13 and 23, and “wherein said diseased or injured body area is inflicted with cancer” in claim 29.

The Examples disclosed in the present specification, in particular, at subsections 6.4 and 7.4, have demonstrated that the direct injection of the target gene sequence (*i.e.*, BMP2) cloned in AAV vector into a skeletal muscle of immuno-competent SD rats results in clear new bone formation at the site of the injection. The Examiner refers to this observation as a “demonstration of inappropriate bone-like structure formation” and states that “the Artisan would not reasonably predict treatment of anything.” Applicants respectfully disagree with the Examiner’s statement. The formation of new bone at the site of direct injection has clearly shown that the orthotopic new bone formation using AAV-based BMP2 vector at the specifically targeted site is highly predictable and would ameliorate the disorders, such as bone fracture non-union, segmental bone defects, spinal fusion, periodontal disease, degenerative disc disease, and growth plate injury. Likewise, other therapeutic genes can be also expressed by a direct administration to a skeletal muscle of the targeted body area and effect their therapeutic effects on a disease or disorder.

Thus, Applicants believe claims 13-15, 23-26, 29-32, 35-39 and 41-47 as amended comply with the enablement requirement under 35 U.S.C. § 112, first paragraph, and, therefore, the rejections of these claims under this section should be withdrawn.

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Applicants believe all the claims are now in condition for allowance, an early notification of which is earnestly requested.

No fee is believed to be due for this submission. Should any fees be required, please charge such fees to Deposit Account No. 50 2215.

Dated: November 16, 2006

Respectfully submitted,

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